

# INTERNATIONAL COOPERATION TREATY

## PCT

### NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
 ETATS-UNIS D'AMERIQUE  
 in its capacity as elected Office

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|--|--|
| <b>Date of mailing (day/month/year)</b><br>15 March 2001 (15.03.01)          |  |
| <b>International application No.</b><br>PCT/GB00/02473                       | <b>Applicant's or agent's file reference</b><br>WPP80900         |
| <b>International filing date (day/month/year)</b><br>28 June 2000 (28.06.00) | <b>Priority date (day/month/year)</b><br>28 June 1999 (28.06.99) |
| <b>Applicant</b><br>GARCIA GRAVALOS, Dolores et al                           |  |

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
 29 January 2001 (29.01.01)

☐ in a notice effecting later election filed with the International Bureau on:  
 \_\_\_\_\_

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

|   |   |
|---|---|
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland<br>Facsimile No.: (41-22) 740.14.35 | Authorized officer<br>Pascal Piriou<br>Telephone No.: (41-22) 338.83.38 |
|---|---|

From the:  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: -

RUFFLES, Graham Keith  
MARKS & CLERK  
57-60 Lincoln's Inn Fields  
London WC2A 3LS  
GRANDE BRETAGNE

PCT

WRITTEN OPINION

(PCT Rule 66)

|   |  |  |
|---|--|--|
| Applicant's or agent's file reference<br>WPP80900   |  | Date of mailing<br>(day/month/year)<br>14.03.2001                |
| International application No.<br>PCT/GB00/02473   |  | REPLY DUE<br>within 3 month(s)<br>from the above date of mailing |
| International filing date (day/month/year)<br>28/06/2000  | Priority date (day/month/year)<br>28/06/1999 |  |
| International Patent Classification (IPC) or both national classification and IPC<br>C07D498/22 |  |  |
| Applicant<br>INSTITUTO BIOMAR S.A.  |  |  |

- This written opinion is the first drawn up by this International Preliminary Examining Authority.
- This opinion contains indications relating to the following items:
  - ☒ Basis of the opinion
  - ☐ Priority
  - ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - ☐ Lack of unity of invention
  - ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - ☐ Certain document cited
  - ☒ Certain defects in the international application
  - ☒ Certain observations on the international application

- The applicant is hereby invited to reply to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).


**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

- The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 28/10/2001.

Name and mailing address of the international preliminary examining authority:

 European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Wörth, C

Formalities officer (incl. extension of time limits)

Brell, S

Telephone No. +49 89 2399 7271



**W...TEN OPINION**International application No. **PCT/GB00/02473****I. Basis of the opinion**

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*).

**Description, pages:**

1-15 as originally filed

**Claims, No.:**

1-18 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

**W... TEN OPINION**International application No. **PCT/GB00/02473**

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 18 with respect to industrial applicability.

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 18.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

## 1. Statement

Novelty (N)                      Claims    Yes: 1-18

Inventive step (IS)              Claims    No: 1-18

Industrial applicability (IA)      Claims    Yes: 1-17

**WRITTEN OPINION**

International application No. PCT/GB00/02473

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2. Citations and explanations  
see separate sheet

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
see separate sheet

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
see separate sheet

**WRITTEN OPINION  
SEPARATE SHEET**International application No. **PCT/GB00/02473****1. Reference is made to the following documents:**

- D1: WO 94 04541 A (SKULNICK HARVEY I ;ABRAHAM IRENE (US); UPJOHN CO (US); ARISTOFF PA) 3 March 1994 (1994-03-03)
- D2: PATENT ABSTRACTS OF JAPAN vol. 018, no. 004 (C-1149), 6 January 1994 (1994-01-06) -& JP 05 247055 A (MEIJI SEIKA KAISHA LTD), 24 September 1993 (1993-09-24)
- D3: T. MEYER ET AL.: 'A derivative of staurosporine (CGP41251) shows selectivity for protein kinase C inhibition and in vitro anti-proliferative as well as in vivo anti-tumor activity', INT. J. CANCER, 1989, vol. 43, pages 851 to 856
- D4: US 5093330 A

The documents D3 and D4 were not cited in the international search report. Copies of the document are appended hereto.

**2. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability (Reference to section III)**

Claim 18 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**3. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement (Reference to section V)****3.1 Novelty**

The subject-matter of the present application differs from the cited prior art in the substituent OR<sup>1</sup> at position 5' of the staurosporine-core.

**Accordingly, the subject-matter of the present application fulfills in view of the cited prior art the requirements of Art. 33(2) PCT.**

**WRITTEN OPINION  
SEPARATE SHEET**

International application No. PCT/GB00/02473

**3.2 Inventive step**

At present, document D3 is considered as closest prior art. This document discloses on page 851, col. 1, abstract, and page 851, col. 2, second paragraph, staurosporine as a potent inhibitor of protein kinase C (PKC) exerting growth inhibition in certain carcinoma cell lines and exhibiting anti-proliferative activity (see table 2, page 853), thereby described as anti-tumor agent (see figure 2, page 854).

In view of this document, the first problem to be solved can be regarded as the provision of staurosporine-derivatives with the same qualitative activity as D3.

The solution to the problem consists in the substitution of staurosporine at position 5' with a radical -OR<sup>1</sup>.

With regard to the technical teaching of document D4, col. 1, line 7 - col. 2, line 29, disclosing tumor-inhibiting staurosporine-derivatives substituted at the methylamino nitrogen, thereby indicating staurosporine as a potential anti-tumor lead-compound, this solution has to be considered as obvious, because the substitution with a radical -OR<sup>1</sup> at position 5' of the staurosporine is at present considered as a minor modification of the known lead compound exhibiting anti-tumor activity (see teaching of D3 in conjunction with D4). Moreover, underlying the principles of structure-activity relationship (SAR), it is stressed that a similar qualitative biological activity can be expected. As a consequence thereof, SAR allows the prediction that for formal analogisations the pharmaceutical activity will be maintained.

Consequently, the further problem to be solved can be regarded as the provision of staurosporine derivatives with unexpected effects. In this context it is noted, that SAR does not allow the prediction as to whether the quantitative biological activity for structurally similar compounds is better or worse. As a consequence thereof, an unexpected effect (e.g. improved antiproliferative activity) can be considered as an indication for inventive step. However, the Applicant has not yet shown, that the claimed compounds are likely to have such an unexpected effect compared to those described in the prior art, in particular the nearest possible compounds, which apparently are represented by staurosporine itself.

**WRITTEN OPINION  
SEPARATE SHEET**

International application No. PCT/GB00/02473

**Accordingly, the present application does not meet the requirements of Art. 33(3) PCT.**

However, it is pointed out, that the technical teaching of document D2 (modification of the terminal amino-group starting from staurosporine results in compounds useful as antiulcer effect enhancer) and document D1 (staurosporine-analogues bearing an oxolan-ring as synergistic enhancers of taxol in killing tumor cells (see page 13, lines 17-19)) indicates, that at least some derivatives of staurosporine can not be considered as anti-cancer agents. Accordingly, the Applicant is invited to give evidence, why the modification of staurosporine with a radical -OR<sup>1</sup> should not be considered as a minor modification.

**3.3 Industrial applicability**

For the assessment of the present claim 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**4. Certain defects of the international application (Reference to section VII)**

- 4.1 To meet the requirements of Rule 5.1(a)(ii) PCT, documents D1-D4 should be identified and the relevant background art disclosed therein should be mentioned.
- 4.2 It is indicated, that the date of deposit of the biological material with the depositary institution has not been mentioned. The Applicant is requested to give the particulars with respect to the deposit of biological material as required in Rule 13bis.2 PCT.

**5. Certain observations on the international application (Reference to section VIII)**

- 5.1 In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments



**WRITTEN OPINION  
SEPARATE SHEET**International application No. PCT/GB00/02473

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by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed. Moreover, the applicant's attention is drawn to the fact that, as a consequence of Rule 66.8(a) PCT the examiner is not permitted to carry out any amendments under the PCT procedure, however minor these may be.

- 5.2 The attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (Article 19(2) and 34(2) PCT). Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application (Article 34(2)(b) PCT).
- 5.3 The Applicant's attention is drawn to the fact that dependent claims are only admissible in the case of a allowable independent claim (cf. Rule 6.4 PCT).

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT  
(PCT Rule 71.1)

To:

RUFFLES, Graham Keith  
MARKS & CLERK  
57-60 Lincoln's Inn Fields  
London WC2A 3LS  
GRANDE BRETAGNE

25 JUL 2001

Date of mailing  
(day/month/year) 23.07.2001

Applicant's or agent's file reference  
WPP80900

IMPORTANT NOTIFICATION

International application No.  
PCT/GB00/02473

International filing date (day/month/year)  
28/06/2000

Priority date (day/month/year)  
28/06/1999

Applicant  
INSTITUTO BIOMAR S.A.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

 European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523658 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer

Brell, S

Tel. +49 89 2399-7271



## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

|   |   |   |
|---|---|---|
| Applicant's or agent's file reference<br><b>WPP80900</b>  | <b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |   |
| International application No.<br><b>PCT/GB00/02473</b>  | International filing date (day/month/year)<br><b>28/06/2000</b>   | Priority date (day/month/year)<br><b>28/06/1999</b> |
| International Patent Classification (IPC) or national classification and IPC<br><b>C07D498/22</b> |   |   |
| Applicant<br><b>INSTITUTO BIOMAR S.A.</b>   |   |   |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

|   |  |
|---|--|
| Date of submission of the demand<br><br><b>29/01/2001</b>   | Date of completion of this report<br><br><b>23.07.2001</b>                             |
| Name and mailing address of the international preliminary examining authority:<br><br> <b>European Patent Office</b><br><b>D-80298 Munich</b><br><b>Tel. +49 89 2399 - 0 Tx: 523656 epmu d</b><br><b>Fax: +49 89 2399 - 4465</b> | Authorized officer<br><br><b>Wörth, C</b><br><br>Telephone No. <b>+49 89 2399 8726</b> |



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**International application No. **PCT/GB00/02473****I. Basis of the report**

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-15 as originally filed

**Claims, No.:**

1-18 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB00/02473

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 18 with respect to IA.

because:

- ☒ the said international application, or the said claims Nos. 18 with respect to IA relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

|                               |                  |
|-------------------------------|------------------|
| Novelty (N)                   | Yes: Claims 1-18 |
|                               | No: Claims       |
| Inventive step (IS)           | Yes: Claims      |
|                               | No: Claims 1-18  |
| Industrial applicability (IA) | Yes: Claims 1-17 |

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. **PCT/GB00/02473**

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No: Claims

2. Citations and explanations  
see separate sheet

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
see separate sheet

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02473

**1. Reference is made to the following documents:**

- D1: WO 94 04541 A (SKULNICK HARVEY I ;ABRAHAM IRENE (US); UPJOHN CO (US); ARISTOFF PA) 3 March 1994 (1994-03-03)
- D2: PATENT ABSTRACTS OF JAPAN vol. 018, no. 004 (C-1149), 6 January 1994 (1994-01-06) -& JP 05 247055 A (MEIJI SEIKA KAISHA LTD), 24 September 1993 (1993-09-24)
- D3: T. MEYER ET AL.: 'A derivative of staurosporine (CGP41251) shows selectivity for protein kinase C inhibition and in vitro anti-proliferative as well as in vivo anti-tumor activity', INT. J. CANCER, 1989, vol. 43, pages 851 to 856
- D4: US 5093330 A

The documents D3 and D4 were not cited in the international search report but cited in the first written opinion.

**2. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability (Reference to section III)**

Claim 18 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**3. Reasoned statement under Art. 35(2) PCT with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement (Reference to section V)****3.1 Novelty**

The subject-matter of the present application differs from the cited prior art in the substituent OR<sup>1</sup> at position 5' of the staurosporine-core.

**Accordingly, the subject-matter of the present application fulfills the requirements of Art. 33(2) PCT in view of the cited prior art.**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02473

**3.2 Inventive step**

Document D3 is considered as closest prior art. This document discloses on page 851, col. 1, abstract, and page 851, col. 2, second paragraph, staurosporine as a potent inhibitor of protein kinase C (PKC) exerting growth inhibition in certain carcinoma cell lines and exhibiting anti-proliferative activity (see table 2, page 853), thereby described as anti-tumor agent (see figure 2, page 854).

In view of this document, the **first** problem to be solved can be regarded as the provision of staurosporine-derivatives with the same qualitative activity as D3.

The solution to the problem consists in the substitution of staurosporine at position 5' with a radical -OR<sup>1</sup>.

With regard to the technical teaching of document D4, col. 1, line 7 - col. 2, line 29, disclosing tumor-inhibiting staurosporine-derivatives substituted at the methylamino nitrogen, thereby indicating staurosporine as a potential anti-tumor lead-compound, this solution has to be considered as **obvious**, because the substitution with a radical -OR<sup>1</sup> at position 5' of the staurosporine is considered as a minor modification of the known lead compound exhibiting anti-tumor activity (see teaching of D3 in conjunction with D4).

Moreover, underlying the principles of structure-activity relationship (SAR), it is stressed that a similar qualitative biological activity can be expected for structurally similar compounds. As a consequence thereof, SAR allows the prediction that for formal analogisations the pharmaceutical activity will be maintained.

Consequently, the **further** problem to be solved can be regarded as the provision of staurosporine derivatives with **unexpected effects**. In this context it is noted, that SAR does not allow the prediction as to whether the quantitative biological activity for structurally similar compounds is better or worse. As a consequence thereof, an unexpected effect (e.g. improved antiproliferative activity) can be considered as an indication for inventive step.

However, the Applicant has not shown, that the claimed compounds are likely to have such an unexpected effect compared to those described in the prior art, in particular the nearest possible compounds, which apparently are represented by staurosporine



**INTERNATIONAL PRELIMINARY**

International application No. PCT/GB00/02473

**EXAMINATION REPORT - SEPARATE SHEET**

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itself.

**Accordingly, the present application does not meet the requirements of Art. 33(3) PCT.**

**3.3 Industrial applicability**

For the assessment of the present claim 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**4. Certain defects of the international application (Reference to section VII)**

- 4.1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, documents D1-D4 are not identified and the relevant background art disclosed therein is not mentioned.
- 4.2 The date of deposit of the biological material with the depositary institution has not been mentioned contrary to the requirements of Rule 13bis.2 PCT.

PCT

REC'D 25 JUL 2001

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

|  |  |   |
|--|--|---|
| Applicant's or agent's file reference<br>WPP80900  | <b>FOR FURTHER ACTION</b>                                | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No.<br>PCT/GB00/02473  | International filing date (day/month/year)<br>28/06/2000 | Priority date (day/month/year)<br>28/06/1999  |
| International Patent Classification (IPC) or national classification and IPC<br>C07D498/22 |  |   |
| Applicant<br>INSTITUTO BIOMAR S.A.   |  |   |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

|   |   |
|---|---|
| Date of submission of the demand<br><br>29/01/2001  | Date of completion of this report<br><br>23.07.2001   |
| Name and mailing address of the international preliminary examining authority:<br><br> European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br><br>Wörth, C<br><br>Telephone No. +49 89 2399 8726<br> |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02473

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-15 as originally filed

**Claims, No.:**

1-18 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02473

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

### III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 18 with respect to IA.

because:

- ☒ the said international application, or the said claims Nos. 18 with respect to IA relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

### V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

|                               |                  |
|-------------------------------|------------------|
| Novelty (N)                   | Yes: Claims 1-18 |
|                               | No: Claims       |
| Inventive step (IS)           | Yes: Claims      |
|                               | No: Claims 1-18  |
| Industrial applicability (IA) | Yes: Claims 1-17 |

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB00/02473

---

No: Claims

2. Citations and explanations  
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/GB00/02473

**1. Reference is made to the following documents:**

- D1: WO 94 04541 A (SKULNICK HARVEY I ;ABRAHAM IRENE (US); UPJOHN CO (US); ARISTOFF PA) 3 March 1994 (1994-03-03)  
D2: PATENT ABSTRACTS OF JAPAN vol. 018, no. 004 (C-1149), 6 January 1994 (1994-01-06) -& JP 05 247055 A (MEIJI SEIKA KAISHA LTD), 24 September 1993 (1993-09-24)  
D3: T. MEYER ET AL.: 'A derivative of staurosporine (CGP41251) shows selectivity for protein kinase C inhibition and in vitro anti-proliferative as well as in vivo anti-tumor activity', INT. J. CANCER, 1989, vol. 43, pages 851 to 856  
D4: US 5093330 A

The documents D3 and D4 were not cited in the international search report but cited in the first written opinion.

**2. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability (Reference to section III)**

Claim 18 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**3. Reasoned statement under Art. 35(2) PCT with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement (Reference to section V)**

**3.1 Novelty**

The subject-matter of the present application differs from the cited prior art in the substituent OR<sup>1</sup> at position 5' of the staurosporine-core.

**Accordingly, the subject-matter of the present application fulfills the requirements of Art. 33(2) PCT in view of the cited prior art.**

### **3.2 Inventive step**

Document D3 is considered as closest prior art. This document discloses on page 851, col. 1, abstract, and page 851, col. 2, second paragraph, staurosporine as a potent inhibitor of protein kinase C (PKC) exerting growth inhibition in certain carcinoma cell lines and exhibiting anti-proliferative activity (see table 2, page 853), thereby described as anti-tumor agent (see figure 2, page 854).

In view of this document, the **first** problem to be solved can be regarded as the provision of staurosporine-derivatives with the same qualitative activity as D3.

The solution to the problem consists in the substitution of staurosporine at position 5' with a radical -OR<sup>1</sup>.

With regard to the technical teaching of document D4, col. 1, line 7 - col. 2, line 29, disclosing tumor-inhibiting staurosporine-derivatives substituted at the methylamino nitrogen, thereby indicating staurosporine as a potential anti-tumor lead-compound, this solution has to be considered as **obvious**, because the substitution with a radical -OR<sup>1</sup> at position 5' of the staurosporine is considered as a minor modification of the known lead compound exhibiting anti-tumor activity (see teaching of D3 in conjunction with D4).

Moreover, underlying the principles of structure-activity relationship (SAR), it is stressed that a similar qualitative biological activity can be expected for structurally similar compounds. As a consequence thereof, SAR allows the prediction that for formal analogisations the pharmaceutical activity will be maintained.

Consequently, the **further** problem to be solved can be regarded as the provision of staurosporine derivatives with **unexpected effects**. In this context it is noted, that SAR does not allow the prediction as to whether the quantitative biological activity for structurally similar compounds is better or worse. As a consequence thereof, an unexpected effect (e.g. improved antiproliferative activity) can be considered as an indication for inventive step.

However, the Applicant has not shown, that the claimed compounds are likely to have such an unexpected effect compared to those described in the prior art, in particular the nearest possible compounds, which apparently are represented by staurosporine

itself.

**Accordingly, the present application does not meet the requirements of Art. 33(3) PCT.**

**3.3 Industrial applicability**

For the assessment of the present claim 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**4. Certain defects of the international application (Reference to section VII)**

- 4.1 Contrary to the requirements of Rule 5.1(a)(ii) PCT, documents D1-D4 are not identified and the relevant background art disclosed therein is not mentioned.
- 4.2 The date of deposit of the biological material with the depositary institution has not been mentioned contrary to the requirements of Rule 13bis.2 PCT.



# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

|  |   |  |
|--|---|--|
| Applicant's or agent's file reference<br><b>WPP80900</b> | <b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |  |
| International application No.<br><b>PCT/GB 00/ 02473</b> | International filing date (day/month/year)<br><b>28/06/2000</b>   | (Earliest) Priority Date (day/month/year)<br><b>28/06/1999</b> |
| Applicant<br><br><b>INSTITUTO BIOMAR S.A.</b>            |   |  |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

**4. With regard to the title,**



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

**5. With regard to the abstract,**



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

**6. The figure of the drawings to be published with the abstract is Figure No.**



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.

=



None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/02473

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D498/22 A61K31/553 A61P35/00 //(C07D498/22,311:00,  
273:00,209:00,209:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, CHEM ABS Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| A          | WO 94 04541 A (SKULNICK HARVEY I ;ABRAHAM<br>IRENE (US); UPJOHN CO (US); ARISTOFF PA)<br>3 March 1994 (1994-03-03)<br>abstract; claim 1<br>page 14 -page 18<br>---  | 1,15-18               |
| A          | PATENT ABSTRACTS OF JAPAN<br>vol. 018, no. 004 (C-1149),<br>6 January 1994 (1994-01-06)<br>-& JP 05 247055 A (MEIJI SEIKA KAISHA<br>LTD), 24 September 1993 (1993-09-24)<br>abstract<br>page 1183; table<br>----- | 1,15-18               |

☐

Further documents are listed in the continuation of box C.

☒

Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

13 October 2000

Date of mailing of the international search report

25/10/2000

Name and mailing address of the ISA

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/GB 00/02473

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---------------------|----------------------------|---------------------|
| WO 9404541 A                              | 03-03-1994          | AU 4787693 A               | 15-03-1994          |
|   |                     | CA 2140653 A               | 03-03-1994          |
|   |                     | EP 0655066 A               | 31-05-1995          |
|   |                     | JP 8500112 T               | 09-01-1996          |
| <hr/>                                     |                     |                            |                     |
| JP 05247055 A                             | 24-09-1993          | NONE                       |                     |
| <hr/>                                     |                     |                            |                     |

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
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PCT

(10) International Publication Number  
WO 01/00627 A1

(51) International Patent Classification<sup>7</sup>: C07D 498/22,  
A61K 31/553, A61P 35/00 // (C07D 498/22, 311:00,  
273:00, 209:00, 209:00, 209:00)

(21) International Application Number: PCT/GB00/02473

(22) International Filing Date: 28 June 2000 (28.06.2000)

(25) Filing Language: English

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(30) Priority Data:  
9915069.0 28 June 1999 (28.06.1999) GB

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(72) Inventors; and

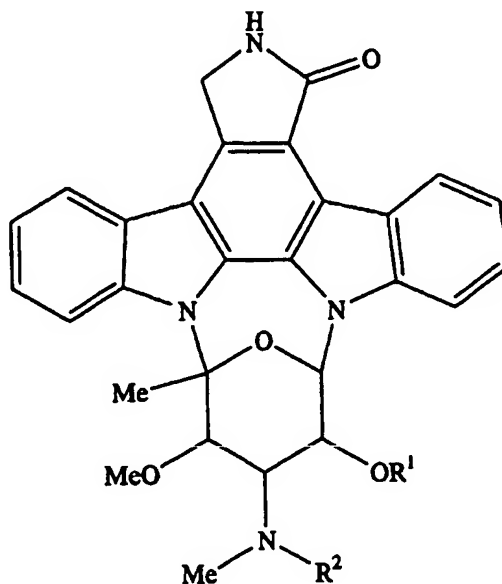
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(81) Designated States (national): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,  
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

[Continued on next page]

(54) Title: NEW INDOLOCARBAZOLE ALKALOIDS FROM A MARINE ACTINOMYCETE



(1)

(57) Abstract: The invention provides compounds of formula (1) wherein R<sup>1</sup> is a hydrogen atom, an alkyl group having 1 to 6 carbon atoms or an alkoxy group having 1 to 6 carbon atoms; and R<sup>2</sup> is a hydrogen atom, an alkyl group having 1 to 6 carbon atoms or an alkoxy group having 1 to 6 carbon atoms; and pharmaceutically acceptable salts thereof. The invention also relates to a process for obtaining the compounds, compositions containing them and their therapeutic use. The compounds display excellent activity against mammalian cancer cell lines.



LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,  
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

# INTERNATIONAL SEARCH REPORT

Inte. onal Application No

PCT/GB 00/02473

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D498/22 A61K31/553 A61P35/00 //(C07D498/22,311:00,  
273:00,209:00,209:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, CHEM ABS Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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|------------|--|-----------------------|
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| A          | PATENT ABSTRACTS OF JAPAN<br>vol. 018, no. 004 (C-1149),<br>6 January 1994 (1994-01-06)<br>-& JP 05 247055 A (MEIJI SEIKA KAISHA<br>LTD), 24 September 1993 (1993-09-24)<br>abstract<br>page 1183; table | 1,15-18               |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

13 October 2000

Date of mailing of the international search report

25/10/2000

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Authorized officer

Paisdor, B

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/02473

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---------------------|----------------------------|---------------------|
| WO 9404541 A                              | 03-03-1994          | AU 4787693 A               | 15-03-1994          |
|   |                     | CA 2140653 A               | 03-03-1994          |
|   |                     | EP 0655066 A               | 31-05-1995          |
|   |                     | JP 8500112 T               | 09-01-1996          |
| JP 05247055 A                             | 24-09-1993          | NONE                       |                     |